7. (twice amended) A method of treating a subject having type C viral hepatitis comprising administering, to the subject, by the peroral route, an oral liquid formulation of natural human α-interferon at a daily dosage of between 100 and 500 IU.

REMARKS

Claims 7, 9, 11, 13, 15, 17 and 20 are pending. The claims are amended, and claim 19 is cancelled, to narrow the issues under consideration so as to put the case in order for allowance, and without prejudice to the prosecution of subject matter, cancelled by amendment, in other patent applications. Revised claim 7, marked to show amendments, is provided on a separate sheet. Also attached is a sheet containing the full set of pending claims.

In the Advisory Action, the Examiner has indicated that amendments made in Applicants' previous response will be entered on the record. The Examiner has maintained the rejections of the claims as obvious under 35 U.S.C §103. For reasons to be set forth in detail below, Applicants request that the claims be allowed to issue.

1. The Claims Are Not Obvious Over The Cummins Citations

Claims 7, 9, 11, 13, 15, 17, 19 and 20 are rejected under 35 U.S.C. §103 as obvious over either one of United States Patent No. 5,824,300 by Cummins ("the '300 patent") or International Patent Application Publication No. WO 88/03411 by Cummins ("the '411 application"), collectively, "the Cummins references".

According to the Examiner, the '300 patent and the '411 application describe aqueous formulations of human interferon which are suitable for use in the

therapeutic methods, wherein the daily dosages disclosed overlap the doses disclosed and claimed in the instant application.

The Applicants respectfully disagree. Currently pending claims 7, 9, 11, 13, 15, 17 are all method of treatment claims, and as such, the intended use is critical to the claims. While the rejection might be applied to a composition claim having, as its only distinguishing limitation, an intended use, it is not applicable here, where the method of using the formulation- for treating viral hepatitis – is patentably distinct from the formulation itself. And, although it is a composition of matter claim, claim 20 has limitations which make the intended use a critical feature of the claim (the composition must comprise a label providing instructions as to the manner of use).

The Cummins references make absolutely no teaching regarding the usefulness of oral α-interferon liquid in treating viral hepatitis. The focus of the '300 patent is not on infectious diseases, but rather on disorders primarily affecting the immune system. It states:

> Interferon contacting the oral and/or pharyngeal mucosa, in amounts of less than 5 IU/lb of body weight per day is consistently effective to potentiate disease-corrective immune responses in vertebrates afflicted with immuno-resistant disease states characterized by apparent hyperactive or hypoactive immune system function. Treatment in accordance with the present invention has been shown to effect remission of neoplastic disease, hyperallergenicity, immuno-resistant or immuno-debilitating viral infections and autoimmune disorders characterized by chronic tissue degenerative inflammation .[1]

Thus, the disclosure of the '300 patent would not suggest the use of its formulations against hepatitis virus, because hepatitis viruses are not disclosed by the reference as

[1] '300 patent, column 3 lines 12-22.

being particularly immuno-resistant or immuno-debilitating. The '300 patent provides examples of viruses which could be treated:

> Exemplary of human viral infections showing remarkable response to treatment in accordance with the present invention are infections of human rhinovirus (common cold), herpes simplex I virus (cold sores) and human papovavirus (warts). Based on treatment results to date, it is expected that contact of interferon at low dosage with the oral and pharyngeal mucosa will provide an effective treatment for Acquired Immune Deficiency Syndrome (AIDS) and disease conditions having the herpes simplex II virus as the causative agent. A patient experiencing a condition of viral myocarditis has responded favorably to the present treatment. Warts often dissipate within six to eight weeks after initiating treatment in accordance with this invention. Interferon administration in accordance with this invention can also be used to help prevent viral infections, for example, infections by the causitive agents of flus and colds, and to minimize the symptoms associated with such viral infections.[2]

Furthermore, the Cummins references focus on the dosage of interferon administered but ignore the formulation, regarding solid, liquid, and gel formulations as being therapeutically equivalent. The present invention, however, is based, at least in part, on the discovery that *liquid* formulations show unexpectedly superior effectiveness. This superior effectiveness is supported by data provided in the Declaration Under Rule 132 submitted with Applicants' previous response. The data compared the effectiveness of oral α-interferon in liquid or tablet form in treating type C viral hepatitis. Patients treated with liquid α-interferon showed an overall response rate of 60%, as compared to rates of 30% in patients treated with α-interferon tablets and 10% in placebo-treated patients. Thus, liquid α-interferon was *twice* as effective as tablet formulations, an advantage completely unexpected in view of the teachings of the Cummins references.

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[2] '300 patent, column 5 lines 12-29.

Applicants invite the Examiner to reconsider the presently claimed invention in view of the background of the invention provided in the specification, which characterizes the state of the art of interferon treatment of hepatitis. Applicants believe that prior art treatment of hepatitis with interferon is a better standard of reference than the Cummins references for assessing the unexpected nature of the present invention, because it relates to hepatitis in particular, whereas Cummins does not relate to hepatitis at all. The specification states:

> **[0005]** Therapeutic cycles consist of alternate day subcutaneous administration of recombinant α-interferon (r α-IFN) at dosages of approximately 5,000,000 UI, that in special cases can be up to 9,000,000 UI/day.
>
> **[0006]** The length of therapeutic cycles is from six months up to one year (nine months average).
>
> **[0007]** In many cases, undesired side effects interfere with the course of therapeutic treatment. In fact some patients, in particular those at an advanced stage of disease or with severe physiologic damage, do not tolerate the therapy and therefore the treatment should be interrupted. Claimed side effects are: fever, nausea, vomiting, tiredness, pain and depression.
>
> **[0008]** Moreover the therapeutic costs are quite relevant due to the high amount of active principle (more than 8,000 new cases each year in Italy and 300,000 world-wide) and to the necessity of hospitalization just in consideration of said side effects further to the parenteral administration (day hospital or outpatient's department).
>
> **[0041]** The therapeutic standard of viral hepatitis C foresees the use of α-interferon through the parenteral route.

In contrast, the presently claimed invention provides a therapy by a more tolerable route (oral versus subcutaneous or intravenous) at substantially lower daily dosages (100 -500 IU versus 5,000,000 -9,000,000 IU), with, consequently, lower cost and fewer side effects. There is nothing in the Cummins references which would suggest to the skilled artisan that a protocol so fundamentally different from the prior art therapy would be effective.

In the Advisory Action, the Examiner indicated that the results presented in the Declaration were not sufficient to constitute objective evidence of non-obviousness of the full scope of the claims. Applicants respectfully disagree, and request the Examiner to consider the success of the low doses used in the study reported in the Declaration, relative to standard therapy. Applicants urge that in view of conventional anti-hepatitis interferon therapy, the results of this study are indeed unexpected. This is especially true in view of the amendment of the claims to pertain to hepatitis C.

It is therefore clear from the specification, and supported by data contained in the 132 Declaration, that hepatitis C may be effectively treated by liquid α-interferon at doses of 100-500IU per day, and that liquid formulations are substantially more effective than tablet formulations. Neither discovery would have been expected in view of the Cummins references. Accordingly, it is respectfully requested that the rejection be removed.

2. The Claims Are Not Obvious Over Cummins And Ratajczak

Claims 9-10 and 15-16 are rejected under 35 U.S.C. §103 over either the '300 patent or the '411 application in view of Ratajczak et al., 1993, Arch. Immunol. Ther. Exp. 41:237-240 ("Ratajczak"). According to the Examiner, Ratajczak discloses the use of lozenges containing 50 or 100 IU of human lymphoblastoid interferon α for oropharyngeal delivery in the treatment of hepatitis B infections, and therefore supplies the deficiency whereby neither Cummins reference teaches lymphoblastoid cell-derived interferon.

Applicants assert that neither the '300 patent nor the '411 patent, alone or in any combination with Ratajczak, would render the claims obvious. None of these

references, considered separately or in combination, would reasonably suggest the two critical features of the instant invention, as presently claimed, namely, (i) the use of α-interferon in *liquid* form in (ii) the treatment of type C viral hepatitis. Ratajczak, in particular, employs lozenges in the treatment of hepatitis B. Hepatitis B virus is structurally and functionally different from hepatitis C. Accordingly, Ratajczak would not lead a skilled artisan to expect that its methods would be useful in the treatment of hepatitis C, much less a different method (liquid versus lozenges). Nor would the addition of the Cummins disclosures change this result, as the Cummins references do not relate to hepatitis B or C.

Therefore, the present rejection should be withdrawn.

3. Conclusion

For all the foregoing reasons, the rejections should be withdrawn and the claims should be allowed to issue. An early allowance is earnestly requested.

Respectfully submitted,

BAKER BOTTS L.L.P.

Lisa B. Kole
PTO Reg. No. 35,225

Anthony Giaccio
PTO Reg. No. 39,684

Attorneys for Applicants
(212) 408-2500

Enclosures

REVISED CLAIMS SHOWING AMENDMENTS

7. (twice amended) A method of treating a subject having type C viral hepatitis comprising administering, to the subject, by the peroral route, an oral liquid formulation of natural human α-interferon at a daily dosage of between 100 and 500 IU.